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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,293	03/16/2005	Cangyou Zhou	21055P	6442

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EXAMINER	
O'DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,293	ZHOU ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *2, 5,7-9,19-21 and 33-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6,10-18 and 22-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :30 December 2007 & 31 August 2007 .

DETAILED ACTION

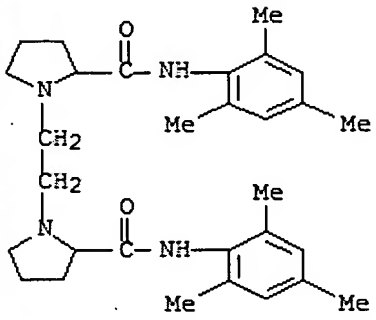
1. This application is a 371 of PCT/US03/33980 filed 10/24/2003 which claims benefit of 60/422,355 filed 10/30/2002.

Claims 1-36 are pending.

Response to Restriction/Election

2. Applicant's election of group IV and the species (the compound of Example 78) in the reply filed on November 30, 2007 is acknowledged. The election was made with traverse, and the examiner finds the arguments persuasive in part and non-persuasive in part. The teaching of Likhosherstov, A. M.; et. al. "Azacycloalkanes. XIX. Synthesis and anesthetic activity of some pyrrolidine-2-carboxylic acid mesidides." *Khimiko-Farmatsevticheskii Zhurnal*, **1976**, 10(7), 36-41 (abstract only) is relevant. Where in formula Ib n is 0, R_6 is $CONR_9R_{10}$, R_9 is H, R_{10} is phenyl (which is substituted by 3 methyl groups), X is $CONR_{10}$, R_{10} is H, m is 1, R_3 is H, R_4 is H, R_5 is H, R_{11} is H, R_{12} is H, R2 is phenyl (substituted by 3 methyl groups), Z is CH2, the compounds of Likhosherstov are produced:

RN 62041-72-9 CAPLUS
CN 2-Pyrrolidinecarboxamide, 1,1'-(1,2-ethanediyl)bis[N-(2,4,6-trimethylphenyl)- (CA INDEX NAME)



which is sufficient to show lack of unity or a special technical feature, however based upon applicant's suggestion Groups IX, X, and XII have been rejoined to Group IV. Moreover the applicant has stated that claims 1, 3, 4, 6, 11, 12, 14-35 read on the elected invention, and this is incorrect. In particular, the claims 33-36 are withdrawn as being drawn to non-elected invention, and claim 19-21 read on R1, which according to the examiner's interpretation must be taken together with W to be a pyrrolidine. It is not clear how these definitions of R1 (in claims 20-21), fit this claim, since they are not open ended (i.e. R1 is CH3). It is not clear either what claim 19 is drawn to as no variable has been pointed out and other ambiguities exist. This application contains claims drawn to a nonelected invention. A complete reply to this action must include a cancellation of nonelected claims or other appropriate action.

Under examination, is group IV, and the new restriction requirement, which has revised groups I—XII is shown below :

Group I, Claims 1-2, 12-32 drawn to compounds and compositions reading on claim 1, Formula I, where W is H, m is 1 or 2, n is 1, Z is C, X is –(C=O)NH-, R2 is benzyl, drawn to piperidinylamino-benzamides, shown as structure **I** in Figure 1. If this group is elected, a

further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group II, Claims 1-2, 12-32 drawn to compounds and compositions reading on claim 1, Formula I, where W is H, m is 1 or 2, n is 0, Z is C, X is –(C=O)NH-, R2 is benzyl, drawn to pyrollidinylamino-benzamides, shown as structure II in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group III, Claims 1-2, 12-32 drawn to compounds and compositions reading on claim 1, Formula I, where W is H, m is 1 or 2, n is 1, Z is O, X is –(C=O)NH-, R2 is benzyl, drawn to morpholinylamino-benzamides, shown as structure III in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group IV, Claims 1, 3, 4, 6, 10-18, 22-32 drawn to compounds and compositions reading on claim 3, Formula Ib or If, m is 1 or 2, n is 1, Z is O or CH, X is –(C=O)NH-, R2 is benzyl, drawn to piperidinyl-pyrollidinyl-benzamides, shown as structure IV in Figure 1, compounds and compositions reading on claim 3, Formula Ib or If, m is 1 or 2, n is 1, Z is NH, X is –(C=O)NH-, R2 is benzyl, drawn to piperazinyl-pyrollidinyl-benzamides, shown as structure IX in Figure 1, compounds and compositions reading on claim 3, Formula Ib or If, m is 1 or 2, n is 0, Z is C, X is –(C=O)NH-, R2 is benzyl, drawn to bis-pyrollidinyl-benzamides, shown as structure X in Figure 1, and compounds and compositions reading on claim 3, Formula Ib or If, m is 1 or 2, n is 2, Z is C, X is –(C=O)NH-, R2 is benzyl, drawn to azepinyl-pyrollidinyl-benzamides, shown as structure XII in Figure 1.

Group V, Claims 1, 5, 12-32 drawn to compounds and compositions reading on claim 5, Formula Ie, m is 1 or 2, n is 1, Z is O, X is –(C=O)NH-, R2 is benzyl, drawn to piperidinyl-isoindolyl-benzamides, shown as structure V in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group VI, Claims 1, 5, 12-32 drawn to compounds and compositions reading on claim 5, Formula Ie, m is 1 or 2, n is 0, Z is O, X is –(C=O)NH-, R2 is benzyl, drawn to pyrrolidinyl-isoindolyl-benzamides, shown as structure VI in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group VII, Claims 1, 5, 12-32 drawn to compounds and compositions reading on claim 5, Formula Ie, m is 1 or 2, n is 1, Z is NR10, X is –(C=O)NH-, R2 is benzyl, drawn to piperazinyl-isoindolyl-benzamides, shown as structure VII in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group VIII, Claims 1-2, 5, 12-32 drawn to compounds and compositions reading on claim 5, Formula Ie, m is 1 or 2, n is absent, Z is absent and R14 and R15 do not form any rings with nitrogen, X is –(C=O)NH-, R2 is benzyl, drawn to amino-isoindolyl-benzamides, shown as structure VIII in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group IX, Claims 1, 7, 8, 10-18, 22-32 drawn to compounds and compositions reading on claim 3, Formula Ib or If, m is 1 or 2, n is absent, Z is absent and R14 and R15 do not form any rings with nitrogen, X is –(C=O)NH-, R2 is benzyl, drawn to amino-pyrollidinyl-benzamides, shown as structure XI in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group X, Claims 1, 3, 7, 8, 10-32 drawn to compounds and compositions reading on claim 3, Formula Ib or If, m is 1 or 2, n is 1, Z is C, X is –(C=O)NH-, R2 is benzyl, drawn to piperidinyl-azetidinyl-benzamides, shown as structure XIII in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group XI, Claims 1-32 remaining compounds drawn to for example compounds and compositions reading on claim 3, Formula Ib or If, m is 1 or 2, n is 1, Z is C, X is –(C=O)NH-, R2 is benzyl, drawn to bis-piperidinyl-benzamides, shown as structure XIII in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election will be made.

Group XII, Claim 33-36, drawn to methods of treating ameliorating, etc. inflammatory or immunoregulatory diseases, classified in class various subclass various, depending on species election, limited in scope to one of the compounds of groups I-XIV. If this group is elected, election of a single disclosed species of compound inflammatory or immunoregulatory disease is required. Further restriction based on the election will be made.

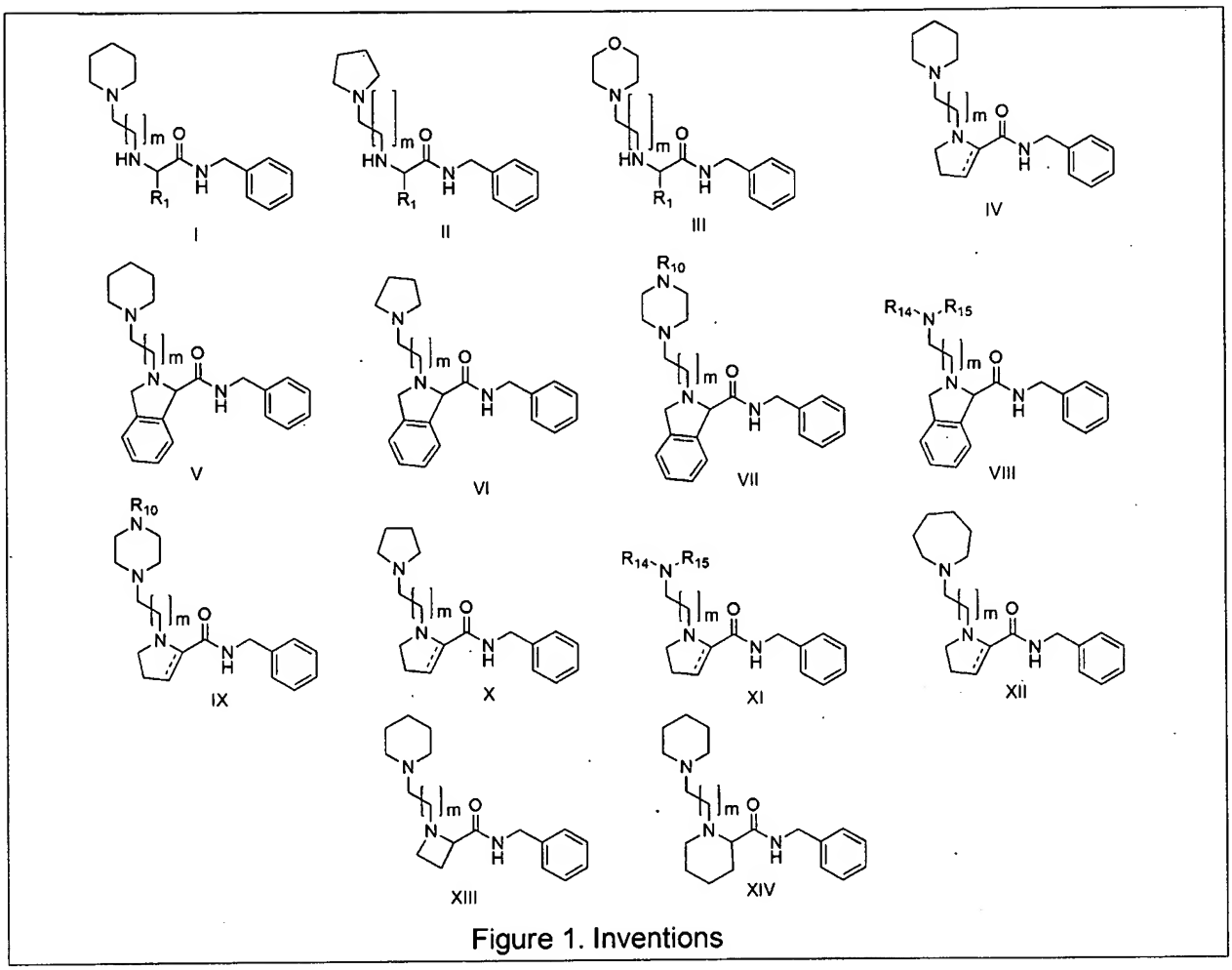


Figure 1. Inventions

Objections

Specification

The disclosure is objected to because of the following informalities: The table containing some the elected compounds is missing some group identities. It is not possibly to determine what these compounds are, a portion is shown below:

68	CO_2Me		H	1	N	509.2
69	Ph		H	1	N	523.2
70			H	1	O	452.2

The spelling of "dedydroproline", on page 51 and other pages is probably meant to be dehydroproline

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 19 does not make sense:

> **19. The compound of Claim 1 wherein -C_{1-6}alkyl, -C_{0-6}alkyl-O-C_{1-6}alkyl-, -C_{0-6}alkyl-S-C_{1-6}alkyl-, and -(C_{0-6}alkyl)-(C_{3-7}cycloalkyl)-(C_{0-6}alkyl), where the alkyl and the cycloalkyl are unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:**

What is meant by "wherein....where"?

Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 31 :

> **31. A compound which is selected from the group consisting of the title compounds of the Examples, and pharmaceutically acceptable salts and individual diastereomers thereof.**

It is unclear what a title compounds is.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 3, 4, 6, 10-18, 22-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds it does not reasonably provide enablement for the scope of compounds bearing the extensive list of substituents. The compounds that are enabled are as follows: In Formula Id R_2, R_3, R_4, R_{11} or R_{12} (the only variables remaining after restriction), R_2 should be limited to benzyl with a very small list of group OH, CO2R, phenyl, benzyl (and perhaps other depending on the identity of the unknown compounds mentioned in the objection).

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing all heterocycles, carbocycles and other groups bearing multiple substitutions of unascertainable structure. **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds and such compounds should have activity at CCR2 receptor. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic/medicinal chemist. **(C) The state of the prior art: (E) The level of predictability in the art: (F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:** Each one of the factors (C, E-H) will be discussed in light of the scientific literature when such a factor is being directly pointed to a large capital letter referring to the aforementioned Wands factor will be placed directly after such a remark or explication. The examiner will first consider the Markush structures Ib and If.

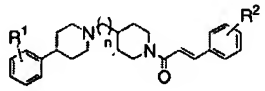
While chemical limitations are important more significantly and more importantly are the limitations of activity at CCR2. What are the important structural features for the claimed utility? It is clear from the data in the specification that the structural features of the compound are of paramount importance for activity. The only information we are given as to what the molecular determinants are for activity at CCR2 receptor is reproduced here:

> **In particular, the compounds of the following examples had activity in binding to the CCR-2 receptor in the aforementioned assays, generally with an IC_{50} of less than about 1 μM. Such a result is indicative of the intrinsic activity of the compounds in use as modulators of chemokine receptor activity.**

While the paucity of compounds in the specification (only 22), and no data make a complete evaluation difficult, all the compounds have two trifluoromethyl group on the benzyl group and very small groups elsewhere (mostly H). **(H)** The medicinal chemistry of CCR2 is relatively well-developed and many limitations are well known in the art. It is sensitive to structural

changes that may be relatively minor in the chemical sense see Xia et. al. "Synthesis and biological evaluation of phenyl piperidine derivatives as CCR2 antagonists" *Bioorganic & Medicinal Chemistry Letters* **2007**, *17*, 5964-5968, whole document. In particular compound **3m** is essentially inactive at 25uM and differs from potent antagonists only by the identity and position of a halogen atom.

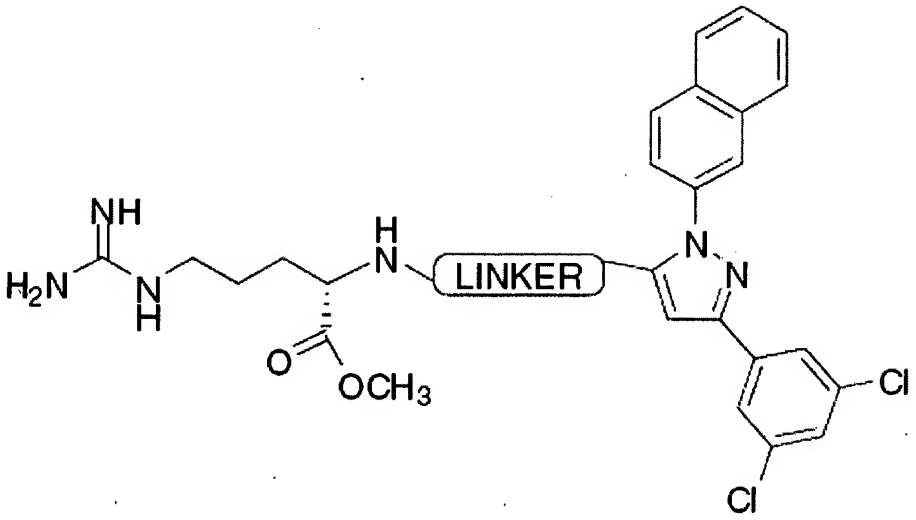
Table 2. Analogs containing a second piperidine ring of structure 3 from Figure 1

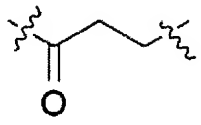
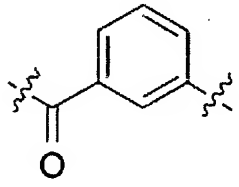
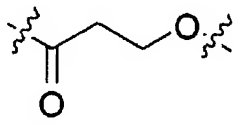


Compound	R^1	*n*	R^2	CCR2B binding IC_{50} (μM)
3a	2-Methoxy	1	3,4-Dichloro	11.1
3b	3-Methoxy	1	3,4-Dichloro	4.0
3c	4-Methoxy	1	3,4-Dichloro	0.32
3d	4-Dimethylamino	1	3,4-Dichloro	0.95
3e	4-Hydroxy	1	3,4-Dichloro	0.51
3f	4-Methyl	1	3,4-Dichloro	2.2
3g	4-Chloro	1	3,4-Dichloro	0.30
3h	4-Chloro	1	3,4-Difluoro	2.0
3j	4-Chloro	1	3,4-Dimethoxy	5.9
3k	4-Chloro	1	3-Trifluoromethyl	1.4
3l	4-Chloro	1	4-Bromo	5.2
3m	4-Chloro	1	2-Fluoro-4-bromo	17% at 25 μM
3n	4-Chloro	2	3,4-Dichloro	2.9

In Anthony B. Pinkerton "Diaryl substituted pyrazoles as potent CCR2 receptor antagonists" *Bioorganic & Medicinal Chemistry Letters* **2007**, *17*, 807–813, a study of structure activity relationships reveals the unpredictable and sensitive nature of CCR2 ligands to the structure of the compound:

Table 2. Linker modifications



Compound	LINKER	CCR2 IC_{50} (nM)[a]	Chemotaxis IC_{50} (nM)
30		4741	NT[c]
31		NA[b]	NT[c]
32		NA[b]	NT[c]
33		62	118

[b] NA denotes not active <10 μM concentration.

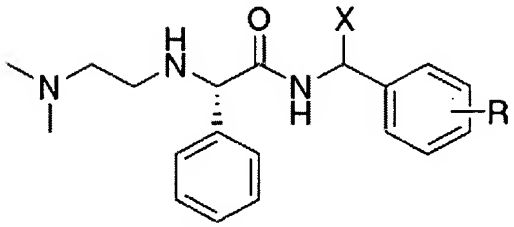
Replacement of an ethyl group in **30** for a phenyl in **32** gave inactive compounds. Where the author stated, "It appears that the SAR is relatively tight for modifications in this area. For example, shortening the chain one carbon, as in **30**, leads to a precipitous drop in activity to 4741 nM. Analog **31** highlights the importance of the central amide for potency—removal of the carbonyl gives a compound that is inactive. Likewise, constraining the linker as in phenyl analog **32** gives an inactive compound."

Perhaps more tellingly are compounds developed by Yang et. al. which are remarkably similar to those of the instant case, Yang et. al. "Discovery of 3,5-bis(trifluoromethyl)benzyl L-arylglycinamide based potent CCR2 antagonists" *Bioorganic & Medicinal Chemistry Letters* **2006**, *16*, 3735–3739. An SAR of the benzylic amide moiety, revealed severe restraints upon the identity of the substituents,

"The **bis-trifluoromethylbenzyl group is extremely sensitive to modification (Table 2). Both of the CF3 groups are critical for activity. Attempts to replace the bis-trifluoromethylbenzyl group with other substituted benzyl groups resulted in inactive compounds (24–27)** as shown in Table 2. The introduction of a methyl at the benzylic position is a way of restricting the number of low-energy conformations at this region, potentially favoring a more active conformation. Unfortunately, in this instance it greatly reduced the binding of compound 28 as compared with the parent 13."

Table 2 is reproduced below for convenience:

Table 2. Binding affinity to human CCR2 (CHO).



Compound	X	R	Binding IC_{50} (nM)
24	H	2-CF_3	1%
25	H	3-CF_3	5%
26	H	4-CF_3	7%
27	H	3,5-DiMe	0%
28	Me	3,5-DiCF_3	28%
13	H	3,5-DiCF_3	1000

% inhibition at 1 μM when no IC_{50}'s were measured.

We have been given no information in regard to the molecular determinants of receptor affinity for the compounds of the instant case, however at least for the bis-CF3 benzyl group the identity cannot be changed and maintain activity. **(F & G)** In this case these compounds bear a remarkable structural resemblance to one another, yet the claims are not commensurate in scope. The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention

that has only 22 examples (that may or may not have activity at CCR2) in this unpredictable art without undue experimentation. **(C, E, F, G, H).**

Conclusion

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

RITA DESAI
PRIMARY EXAMINER

1/17/08